J. Chem. Thermodynamics 73 (2014) 171–177

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

Proton affinity and gas-phase basicity of hydroxyquinol: A computational study

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ARTICLE INFO

Article history:
Available online 22 December 2013

Dedicated to the memory of the late Professor Manuel Ribeiro da Silva

Keywords:
1, 2, 4-Benzenetriol
1, 2, 4-Trihydroxybenzene
Alternate sites of protonation
Calixarenes
Macrocycles
Resorcinarenes
G4(MP2)

ABSTRACT

Hydroxyquinol (1,2,4-trihydroxybenzene) exhibits a variety of activities of interest to the biomedical and organic chemist. In the particular, hydroxyquinol has numerous possible non-equivalent sites for protonation and reaction with other electrophiles. High level DFT and conventional *ab initio* quantum chemical calculations, diverse isodesmic proton transfer reactions, and qualitative understanding, of both intramolecular hydrogen bonding and carbocation stability, are used to explain the energy and geometry changes, and the location (which carbon or oxygen) associated with the still unmeasured proton affinity and gas-phase basicity of this species. Application is made to the synthesis of still unknown calixarene-related macrocycles.

1. Introduction

The proton affinity (PA) and gas-phase basicity (GB) of a molecule are useful thermochemical data to understand its reactivity, as many chemical and biochemical reaction pathways are initiated by or involve a proton transfer. PAs and GBs have therefore been the focus of a number of reviews (see, for example, References [1–11] and references cited within), and have also been of interest to our groups for some time [12–22]. The protonation of benzene, polysubstituted benzenes and other aromatics has been the focus of a number of research articles, *e.g.* [23–28]. Of particular interest to this work is the protonation of trihydroxybenzenes. Although the protonation of phenol has been studied extensively both experimentally and theoretically [11,29–33], there have been fewer studies involving the protonation of di- and trihydroxybenzenes [31,32,34]. In this work, we evaluate the PA and GB of hydroxyquinol, more properly named 1,2,4-trihydroxybenzene or 1,2,4-benzenetriol.

Hydroxyquinol has several roles in biological systems. The most prevalent pathways in which hydroxyquinol plays a role involve microbial degradation, where hydroxyquinol is formed by either resorcinol or chloro-substituted di- or trihydroxybenzenes and subsequently forms maleylacetate or 2,4-dihydroxymuconic semialdehyde [35,36]. Hydroxyquinol and chlorohydroxyquinol are also substrates for hydroxyquinol-1,2-dioxygenases of the 2,4,6-trichlorophenol-degrading strains in the bacterium *Cupriavidus necator* [36].

Although the preferred site of protonation has been determined experimentally for the trihydroxybenzenes [34], no PAs or GBs were reported in this study. In fact, to our knowledge, the PAs and GBs of these species have not been determined experimentally or computationally. However, the neutral trihydroxybenzenes have been investigated with respect to (1) the hydrogen-bonding interactions between water and 1,3,5-trihydroxybenzene [37], (2) the interactions between 1,3,5-trihydroxybenzene dimers [38], (3) the relative stabilities of the di- and trihydroxybenzenes [39], (4) the interconversion between 1,2,3- and 1,3,5-trihydroxybenzene (pyrogallol and phloroglucinol, respectively) through anaerobic degradation [40], and (5) the enthalpies of formation of pyrogallol, phloroglucinol and hydroxyquinol [41].

A complementary theoretical and experimental study by Bouchoux *et al.* determined the proton affinity of both mono- and dihydroxybenzene(s) and good agreement between the calculations and experiment was observed [31]. The most stable protonation site in all cases is a carbon that is *para* and/or *ortho* to a hydroxy group, while protonation of an oxygen is less favored. In general, formation of intramolecular hydrogen bonds and protonation at a *para* position is favored, whereas in the case of hydroquinone, 1,4-dihydroxybenzene, only protonation at an *ortho* position is observed. Their calculations show that protonation of an oxygen

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http://dx.doi.org/10.1016/j.jct.2013.12.015

atom is approximately (60 to 70) kJ · mol^{-1} less stable than protonation at the most favored carbon site. This result supports the finding by Defrees *et al.* that the PA of the oxygen in phenol is (55 to 85) kJ · mol^{-1} smaller than that of a site on the ring [29]. In the earlier experimental studies by Olah and Mo, super-acids were used to elucidate the preferred protonation sites for mono-, di- and trihydroxybenzenes, via both ^{1}H and ^{13}C NMR [32,34]. The most favorable carbon-protonated species calculated by Bouchoux and co-workers [31] agree with the carbon-protonated species identified by Olah and Mo.

In previous theoretical investigations of the protonation of substituted aromatic systems [1,5,7–9,24–31,39,42–46], the calculational methods ranged from HF and DFT to MP2 to QCISD and CCSD(T), and these methods were combined with a variety of double- and triple-zeta basis sets. In fact, gas-phase acidities and basicities evaluated with DFT methods and a valence triple-zeta basis set augmented with polarization functions on the heavy atoms, *e.g.*, B3LYP/6-311 + G(d,p), have been found to be within chemical accuracy for the series of acids and bases investigated by Burk and co-workers [47]. In this study, we have also employed a variety of methods and basis sets. Specifically, geometries have been optimized with the DFT hybrid functionals B3LYP [48,49] and ωB97X-D [50], which includes empirical dispersion, and the LANL2DZ and aug-cc-pVTZ basis sets. PAs have been obtained with the MP2, M05-2X [51] and ωB97X-D methods in conjunction with the aug-cc-pVTZ basis set and with the G4(MP2) method [52]. The lower-level B3LYP/LANL2DZ and ωB97X-D/LANL2DZ optimizations have been included in the study because of our interest in extending the PA and GB calculations to supramolecular host–guest complexes for which a hydroxybenzene comprises the framework of the constituent macrocycles or acts as a guest [53–57]. Previous studies have revealed host–guest complexes of hydroxyquinol (guest) with pyridinyl macrocycles [58]. Given the presence of the hydroxyl groups, introduction of hydroxyquinol into existing macrocycles or metal-seamed/hydrogen-bonded capsules as a possible gate or an exo-guest for metal coordination is possible [59]. In this study of a possible building block for supramolecular host–guest complexes, in addition to determining the PA of hydroxyquinol and the preferred site of protonation, we also (1) determine the difference in PA for oxygen *vs.* carbon protonation, (2) examine the effect of loss or enhancement of intramolecular hydrogen bonding on the magnitude of the PA and (3) gain insight into the cyclization of hydroxybenzenes to form macrocycles.

2. Computational details

All calculations were carried out using the Gaussian09 suite of programs [60] and the results were visualized with Gaussview5 [61]. The geometries of hydroxyquinol and protonated hydroxyquinol were optimized completely at the B3LYP/LANL2DZ, ωB97X-D/LANL2DZ and ωB97X-D/aug-cc-pVTZ levels of theory with the int = ultrafine and opt = tight keywords. For the rest of this article, the aug-cc-pVTZ basis set will be abbreviated aVTZ. Minima were confirmed and thermochemical corrections were obtained via normal-mode vibrational frequency analyses. Single-point energies (SPEs) were evaluated at the MP2/aVTZ, M05-2X/aVTZ and ωB97X-D/aVTZ calculational levels, where applicable. The thermochemical data obtained at the two lower calculational levels have been benchmarked against the MP2/aVTZ//ωB97X-D/aVTZ data. Because the Gn(MP2) methods have been shown to provide reliable PAs for hydroxybenzenes [31], PAs and GBs for selected systems have also been evaluated with G4(MP2) theory [52].

In order to locate all stable minima and unique protonation sites for hydroxyquinol, starting geometries with all possible arrangements of the hydroxyl hydrogen atoms, both in and out of the plane, for the neutral molecule were optimized at the B3LYP/LANL2DZ level of theory. The equilibrium geometries located were subsequently re-optimized at the ωB97X-D/LANL2DZ and ωB97X-D/aVTZ levels of theory. All possible protonation sites were examined for the six stable neutral conformations identified, and protons were oriented both in and out of the plane for protonated O—H sites. The same protocol for optimizations was carried out as was described above for the neutral species. Cartesian coordinates for all neutral and protonated complexes optimized at the ωB97X-D/aVTZ level of theory can be found in table S1, and complete energetic results for all optimization and SPE calculations can be found in table S2.

PAs at 298 K can be determined by equations (1) and (2) or, written more simply, as $-\Delta_{rx}H_{298}$ for reaction (3). The GB is given by $-\Delta_{rx3}G_{298}$. Recall that $E_T(H^+) = 0$ and that $E_T(B^{n-1})$ and $E_T(HB^n)$ are the total energies of the base (B) and its protonated form (BH^+). Also, the changes for the reaction in the translational, rotational and vibrational energy differences between temperatures (298 and 0) K are denoted by ΔE_x where $x = t$, r and v, respectively. The change in the zero-point vibrational energies of the reactants and products is given by ΔZPE and ΔpV is the change in the pV work term. PAs can also be predicted by the proton-transfer reaction given in equation (4), using the experimental PA value for base B_2 [7,8,11]. Reaction (4)is isodesmic when both bases are protonated on carbon or when both bases are protonated on oxygen.

$$PA = \Delta E^0 + \Delta E_t^{298} + \Delta E_r^{298} + \Delta E_v^{298} + \Delta pV, \quad (1)$$

$$\Delta E^0 = [E_T(B^{n-1}) + E_T(H^+) - E_T(HB^n) + \Delta ZPE], \quad (2)$$

$$B + H^+ \rightarrow BH^+, \quad (3)$$

$$B_1H^+ + B_2 \rightarrow B_1 + B_2H^+. \quad (4)$$

3. Results and analysis of results

3.1. Neutral species

Of the six equilibrium structures located for neutral hydroxyquinol, all of which are planar and have C_S symmetry, the four most stable isomers A–D exhibit O—H···O intramolecular hydrogen bonding and have relative enthalpies within 4 kJ · mol^{-1} (tables 1 and S3). By contrast, the remaining two isomers E and F exhibit no hydrogen bonding, have lone pairs facing each other on the 1- and 2-oxygens, and are sensibly (15 to 20) kJ · mol^{-1} less stable at the MP2/aVTZ//ωB97X-D/aVTZ level of calculation (figure 1). In fact, the relative enthalpies and free energies at a given calculational level (*e.g.*, MP2/aVTZ//B3LYP/LANL2DZ, MP2/aVTZ//ωB97X-D/LANL2DZ and MP2/aVTZ//ωB97X-D/aVTZ) vary by less than 1 kJ/mol and for a given geometry (*e.g.*, MP2/aVTZ//B3LYP/LANL2DZ, M05-2X/aVTZ//B3LYP/LANL2DZ and ωB97X-D/aVTZ//B3LYP/LANL2DZ) vary by less than 2 kJ · mol^{-1} (tables 1 and S3). In a previous study of hydroxyquinol, Mammino and Kabanda

TABLE 1
Relative enthalpies and free energies of hydroxyquinol.

Complex	ΔH/(kJ · mol^{-1})[a]	ΔG/(kJ · mol^{-1})[a]
A	0.0	0.0
B	0.2	0.8
C	0.4	0.5
D	3.7	3.8
E	16.4	16.8
F	18.8	18.9

[a] MP2/aVTZ//ωB97X-D/aVTZ data.